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Myocardial Perfusion Defect on Thallium-201 Imaging in Patients With Chronic Obstructive Pulmonary Disease

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Six patients with angina pectoris had reversible perfusion defects on stress and redistribution thallium imaging. Three patients had a positive electrocardiographic response to exercise. No significant coronary artery lesions were seen on coronary arteriography in any of the six patients. All had mild to moderate hypoxemia at rest and physiologic evidence of chronic obstructive pulmonary disease as defined by the decrease in the ratio of forced expiratory volume at 1 second to forced vital capacity ($FEV_1/FVC \times 100$) or decrease in the forced midexpiratory flow rate (FEF_{25-75}), or both. None had clinical findings suggestive of any of the reported causes of positive thallium scans in patients with normal coronary arteriograms. Cellular dysfunction produced by hypoxemia affecting the uptake of thallium seems to be the most likely mechanism of this abnormality.

The use of thallium-201 myocardial imaging for detection of fixed obstructive coronary artery disease is well established (1–5). There are, however, several reported causes of defects on thallium imaging in patients with normal coronary arteriograms. These include sarcoidosis (6–8), overlying soft tissues (9,10), aortic valve stenosis (11), myocardial bridges (12,13), coronary anomalies (14), idiopathic congestive cardiomyopathy (15) and coronary artery spasm (16). Conflicting data have been reported concerning the effect of mitral valve prolapse on the thallium-201 myocardial scan (17–22). The perfusion scan may also be sensitive to a lesion not seen on the coronary arteriogram, especially if an adequate number of views is not taken (23). To this list, we should add the variations in radionuclide uptake as seen in some normal subjects (24). It has also been suggested that disordered cell function might result in an abnormal myocardial image (25).

We present six patients with pulmonary insufficiency and hypoxemia as probable causes of myocardial cellular dysfunction with resulting reversible defects on thallium imaging.

Methods

Study patients. The six patients were seen at Howard University Hospital from May 1980 to August 1981. Their mean age was 55 years (range 41 to 66); two were men and four were women. All patients experienced sufficient symptoms to warrant contrast coronary and ventricular angiography. Studies were obtained during the course of routine evaluation of chest pain. In all patients the chest pain was typically anginal in nature. In addition, two patients had episodes of chest pain that were atypical in terms of precipitating factors.

No patient had sustained a previous myocardial infarction or had evidence of valvular heart disease, mitral valve prolapse, collagen vascular disease, primary cardiomyopathy or sarcoidosis. One patient had insulin-dependent diabetes mellitus. Four patients were hypertensive, but none had evidence of left ventricular hypertrophy by M-mode echocardiography or by electrocardiographic criteria. Three patients were cigarette smokers, and three did not smoke.

Cardiac and pulmonary evaluation. Diagnostic cardiac catheterization was performed in each patient using the Judkins technique. Multiple views of selective coronary cineangiography were obtained. Contrast left ventriculography was performed in the 30° right anterior oblique projection at rest. Hemodynamic data were obtained using standard techniques. Coronary angiograms and ventriculograms were reviewed independently by three experienced angiographers, and all studies were judged to be of diagnostic quality.

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M-mode echocardiograms were obtained in all patients and were normal. There was no evidence of mitral valve prolapse, asymmetric septal hypertrophy, valvular abnormalities or left ventricular hypertrophy.

The 12 lead electrocardiogram at rest was normal in all patients. There was no electrocardiographic evidence of myocardial infarction, left ventricular hypertrophy, arrhythmias or conduction abnormalities.

Pulmonary function studies were done within 1 month of cardiac catherization. Spirometry was performed on an M-100B automated pulmonary function laboratory (Gould/SRL Medical). Predicted normal values were derived from the Veterans Administration Armed Forces cooperative study (26).

Exercise protocol. Medications, not discontinued before exercise, included nitrates, diuretic drugs and various antihypertensive medications. One patient was taking digoxin. No patient was taking propranolol or any antiarrhythmic agent. The thallium exercise studies were done within 1 month of cardiac catheterization in four patients. One patient underwent cardiac catheterization within 6 months and another within 8 months of the thallium exercise study. Electrocardiograms were monitored during exercise with a CM_5 lead on a Quinton Instruments model 621B electrocardiographic recorder. Heart rate, electrocardiogram and cuff blood pressure were obtained at rest and at 1 minute intervals during exercise which was performed on a Quinton model 18-49-C treadmill using a standard Bruce protocol. All six patients exercised until limiting fatigue or dyspnea occurred. Five of the six patients attained at least 85% of their predicted maximal heart rate. One patient developed severe dyspnea after 3 minutes of exercise.

Thallium-201 perfusion imaging. At peak exercise, 1.5 to 2.0 mCi of 201 thallous chloride (Mallinckrodt) was injected through an indwelling intravenous catheter. Exercise was continued at peak level for 60 seconds after injection. Electrocardiographic tracings were recorded for 3 minutes into the recovery period. Imaging with a General Electric Maxicamera II interfaced with a Medical Data Systems A2 multiterminal computer system was begun within 10 minutes of the termination of exercise. Images were acquired with the patient in the supine position and the detector head positioned to obtain anterior and 40 and 60° left anterior oblique views. Each image was acquired for a total of 300,000 counts. Redistribution images were obtained 3 hours after injection. Camera angles were recorded for each patient to assure duplication of position during the redistribution study.

Interpretation of data. Both analog and digital images were obtained. Stress and redistribution digital images were displayed side by side, and preliminary interpretation at the computer terminal was made by one observer. Hard copy digital images were obtained side by side from the stress and redistribution display with the gray scale adjustment made by visual assessment of image quality on the anterior view. The general range represented the equivalent of 10 to 20% background subtraction with approximately 204 gray levels. Left anterior oblique 40 and 60° views were photographed at the same settings. Hard copy data were displayed using single emulsion film and videotape. Interpretation was based on consensus of opinion by both methods. Little interobserver variability was noted in 300 clinical cases evaluated by this method.

Results

Pulmonary function studies. All patients had chronic obstructive pulmonary disease as defined by a decrease in the ratio of forced expiratory volume at 1 second to forced vital capacity ($FEV_1/FVC \times 100$) or a decrease in the forced midexpiratory flow rate (FEF_{25-75}), or both (Table 1). The $FEV_1/FVC \times 100$ ranged from 67 to 74 (mean 66.5). The percent predicted FEF_{25-75} ranged from 32 to 69% (mean 51). All patients also exhibited hypoxemia at rest as evidenced by lowered partial pressure of oxygen in arterial blood (Po2) and widened alveolo-arterial oxygen gradients ($A\text{-}aD_{O2}$). The P_{O_2} at rest ranged from 61 to 84 mm Hg

Table 1. Respiratory Function Studies

Case	Smoking History (pack-years)	pH	P_{O_2} (mm Hg)	P_{CO_2} (mm Hg)	$FEV_1/FVC \times 100$	FEF_{25-75} (liters/min)	% Predicted FEF_{25-75}	$A\text{-}aD_{O2}$ (mm Hg)
1	0	7.37	84	45	64	117	60	13
2	10.5	7.36	80	44	66	94	63	18
3	0	7.37	72	39	66	96	41	30
4*	80	7.42	81	36	74	106	69	27
5	0	7.45	77	29	64	70	36	39
6	13	7.42	61	47	65	52	32	34

*These values were obtained while the patient was receiving bronchodilator therapy.

$A\text{-}aD_{O_2}$ = alveoloarterial oxygen difference; FEF_{25-75} = forced midexpiratory flow rate; FEV_1 = forces expiratory volume at 1 second; FVC = forced vital capacity; pH = 1/log hydrogen ion concentration; P_{CO_2} = partial pressure of carbon dioxide, P_{O_2} = partial pressure of oxygen.

Table 2. Clinical Characteristics

Case	Age(yr) & Sex	Respiratory Symptoms	ST Segments During Exercise	Angina	Coronary Angiogram
1	53M	None	→	Yes	Normal
2	66F	None	↓ 4 mm	Yes	Normal
3	44M	Mild exertional dyspnea	↓ 2 mm	Yes	Normal
4	62F	None	→	Yes	Minimal luminal irregularities mid-RCA
5	41F	Recurrent bronchospasm	→	Yes	Normal
6	53F	Mild exertional dyspnea	↓ 1 mm	Yes	Normal

F = female; M = male; RCA = right coronary artery; ↓ = ST segment depression during exercise; → = no ST segment changes during exercise.

(mean 76), while the A-aD_{O_2} ranged from 13 to 39 mm Hg (normal ≤ 10).

Cardiac features. The symptomatic state varied from asymptomatic or mild exertional dyspnea in five patients to recurrent bronchospasm in one patient (Table 2). Each patient had a history of angina pectoris. The stress electrocardiographic response varied and was positive in three patients. No patient had ST segment elevation either at rest or during exercise. Review of the angiographic data revealed normal position and caliber of each major coronary vessel and its branches. There was no evidence of obstructive coronary stenosis. No patient had mitral valve prolapse, regional wall motion abnormality, compression of septal perforator branches or myocardial bridging. One patient had minimal luminal irregularities in the midportion of the right coronary artery. Pulmonary artery, left ventricular and systemic arterial pressures were all normal at the time of catheterization.

Thallium imaging abnormalities. All six patients had reversible perfusion defects on thallium-201 scanning. These areas showed redistribution of counts on the 3 hour postinjection scan. The segments involved varied from patient to patient and multiple segments were involved in each patient (Table 3). Defects were seen in more than one view in all patients and were not confined to any particular coronary artery distribution.

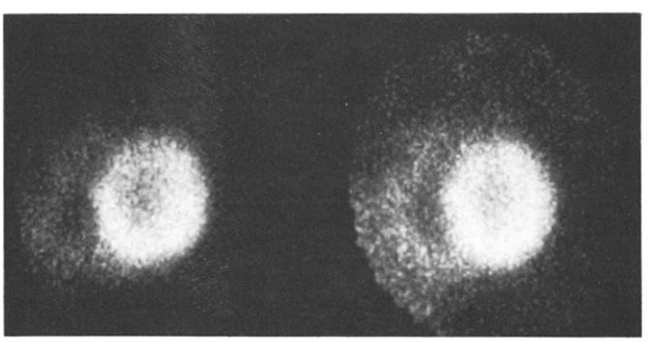
Figure 1 shows stress and redistribution thallium scintigrams obtained from Patient 1. Diminished uptake of thallium is noted in the septum during stress. This defect shows resolution on the redistribution images. The right ventricular uptake of thallium is also increased on the follow-up scintigram. Figure 2 demonstrates stress and redistribution thallium scintigrams obtained from Patient 2. Reversible defects involving the septum is shown. A striking transmural septal defect is seen in Figure 3 (Patient 3). This was accompanied by decreased thallium uptake in the anterior and inferior segments. All areas showed resolution of the defects 3 hours later. The right ventricular thallium uptake is also more marked on the redistribution image. Although the target to background ratio is low in Figure 4 (Patient 4), diminished thallium uptake is apparent in the inferior and anterolateral segments. Both areas show increased thallium uptake 3 hours later on the follow-up scintigram. Analog images of Patient 5 are shown in Figure 5. Reversible defects are noted in the

Table 3. Location of Segmental Perfusion Defects on Thallium Imaging

Case	Ant View	LAO 40°	LAO 60°
1	—	Septal	Ant-Lat
2	—	Septal	Post-Basal
3	Ant-Inf	Septal	Ant-Lat, Inf
4	Inf	—	Ant-Lat, Inf
5	Ant	—	Ant-Lat, Inf
6	Ant	Posterolateral	Ant-Lat

Ant = anterior; Inf = inferior; LAO 40° and LAO 60° = 40° and 60° left anterior oblique view, respectively; Lat = lateral; Post = posterior.

Figure 1. Patient 1. Stress **(left)** and redistribution **(right)** thallium scintigrams in the 40° left anterior oblique view. There is decreased uptake of thallium in the septum during stress. The redistribution image shows increased thallium uptake in this area. The right ventricular uptake is also increased on the redistribution image.



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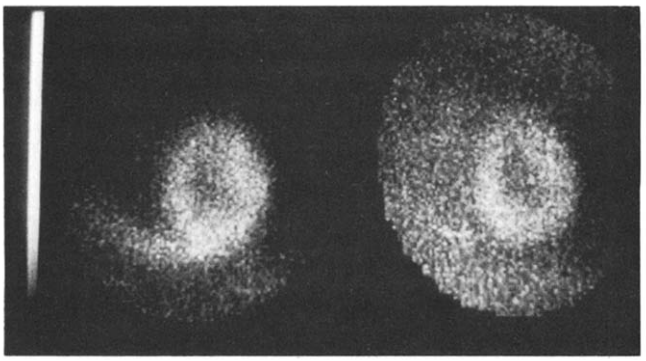


Figure 2. Patient 2. Stress **(left)** and redistribution **(right)** thallium scintigrams in the 40° left anterior oblique view. Thallium uptake in the septum is diminished during stress with resolution occurring on the redistribution image.

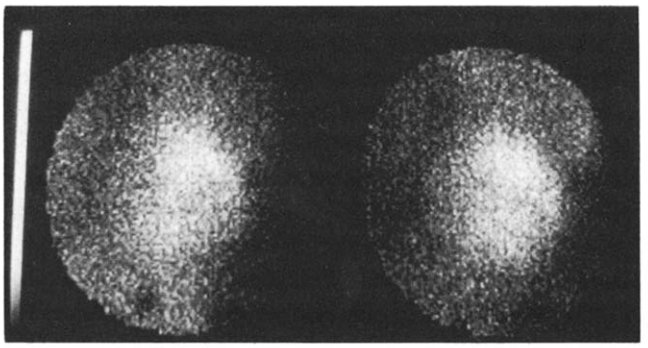


Figure 4. Patient 4. Stress **(left)** and redistribution **(right)** thallium scintigrams obtained in the anterior view. There is decreased uptake of thallium in the inferior and anterolateral segments during stress. The redistribution image reveals increased uptake in these areas.

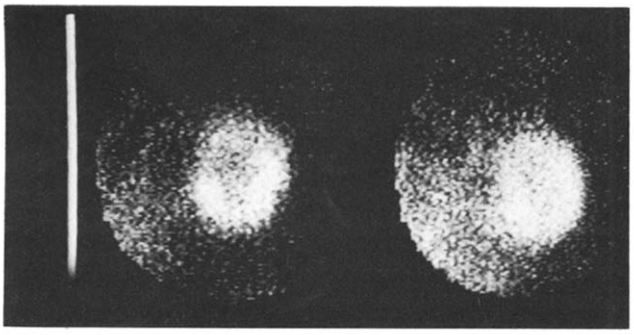
anterior and inferior segments. Figure 6 demonstrates stress and redistribution images obtained from Patient 6. Anterolateral reversible defect is apparent.

Discussion

The myocardial uptake of a potassium analog such as thallium is related to both regional myocardial blood flow and active transport of these agents across the cell membrane (27–29). The uptake of thallium thus reflects capillary surface area, membrane permeability and blood flow. The transport of thallium across the cell membrane has been shown to be dependent on an active sodium-potassium adenosine triphosphatase (ATPase) system (30,31). The latter reflects the integrity of the cell membrane concentrating mechanism.

Myocardial thallium uptake in hypoxia. Levenson et al. (32) reported evidence that the uptake of thallium by the sarcolemma might be reduced by hypoxia independent of blood flow. Regional hypoxia was produced in dogs by maintaining perfusion with hypoxemic venous blood. Scintigrams were produced using cesium-129, another potassium analog. These authors noted defects in the scintigrams corresponding to the cyanotic area with complete resolution of the defects after arterial reperfusion. In 1977, Weich et al. (33) reported a significant decrease in the myocardial extraction of thallium in dogs made hypoxic by ventilation with gas mixtures low in oxygen content. Hypoxia caused a significant decrease in the extraction fraction from 88 ± 2.1% at the basal level to 77.9%. Hypoxia causes a marked decrease in the activity of the sodium-potassium ATPase pump (33) and would thus be expected to result in a decrease in thallium extraction.

Figure 3. Patient 3. Stress **(left)** and redistribution **(right)** thallium scintigrams in the 40° left anterior oblique view. During stress, thallium uptake in the septum is decreased. Resolution of the defects is apparent on the redistribution scan. There is also a slight increase in right ventricular uptake on the redistribution image.



Myocardial hypoxia in chronic obstructive pulmonary disease. The coronary arteriograms in our six patients show no evidence of obstructive lesions. Thus, there is nothing to suggest impairment of flow. However, all patients had mild to moderate degrees of hypoxemia at rest in the presence of physiologic evidence of chronic obstructive pulmonary disease. Previous studies (34–36) demonstrated that many patients with chronic obstructive pulmonary disease develop significant exertional hypoxemia. Minh et al. (35) concluded that hypoxemia could not be predicted on the basis of gas exchange indexes observed at rest. This decrease in arterial saturation would occur in the face of increased myocardial oxygen requirements during exercise. The resulting myocardial hypoxia would then lead to impairment of active membrane function with reduced uptake of thallium. We believe that this might be the mechanism of reduced myocardial uptake of thallium in our patients with normal coronary arteriograms.

One might expect to find evidence of global rather than segmental abnormalities in thallium uptake if our hypothesis is correct. Indeed, the abnormality may be global. However, with thallium, each segment is compared with others in the same image, there being no "normal" for each image. Thus,

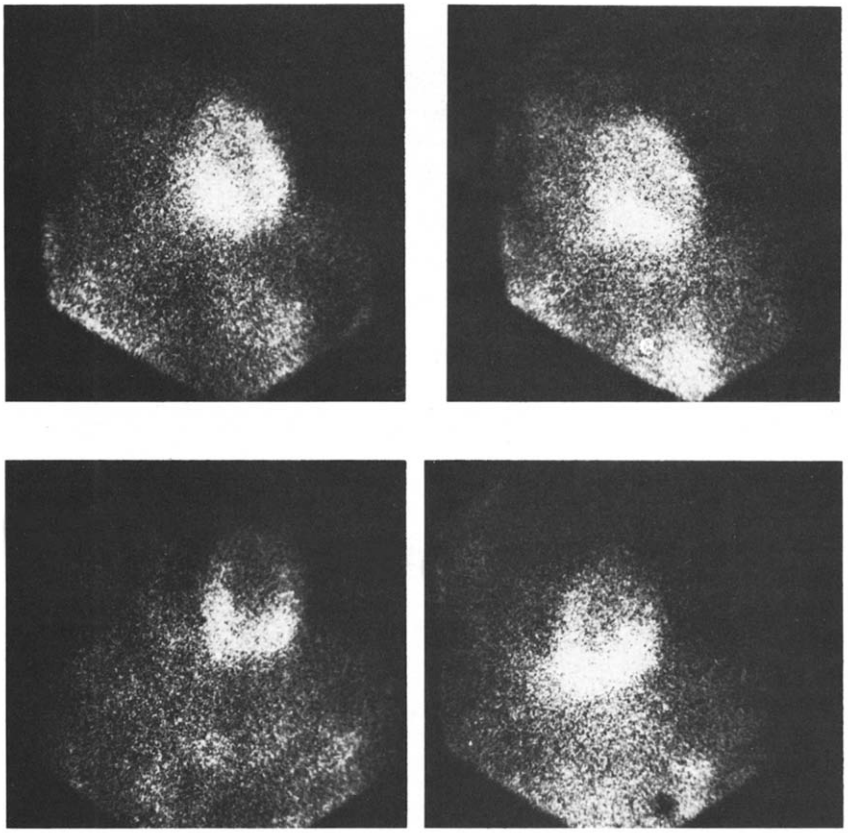


Figure 5. Patient 5. Stress **(left panels)** and redistribution **(right panels)** thallium scintigrams obtained in the anterior **(upper panels)** and 60° left anterior oblique **(lower panels)** views. Uptake of thallium is diminished in the anterior and inferior segments during stress. Increased uptake in these areas is apparent on the redistribution image.

only those segments most severely affected would be obviously abnormal, while those less affected may appear normal.

Role of acidosis. Severe acidosis (pH 7.02) has also been reported to cause diminished extraction of thallium (33). In the series reported by Minh et al. (35), arterial pH decreased during maximal exercise. However, exertional acidosis was not observed. Although arterial blood gas analysis was not done during exercise in our patients, we believe that acidosis would be an unlikely mechanism to explain their abnormalities in thallium uptake.

Role of coronary spasm. Though rare, exercise-induced coronary artery spasm has been observed (37–40). Berger et al. (41) reported on 31 patients with chest pain, ischemic changes on exercise electrocardiography and angiographically normal coronary arteries who were evaluated using first pass radionuclide studies. Five patients in their group had exercise-induced thallium-201 perfusion defects. No patient who underwent ergonovine provocation showed evidence of coronary artery spasm. The status of pulmonary function in this group was not reported. Because ergonovine provocation was not performed in our patients, the possibility of spasm cannot be completely excluded.

Myocardial ultrastructural abnormalities. These were demonstrated by Lösse et al. (42), in patients with abnormal thallium scans and normal coronary arteries. Right ventric-

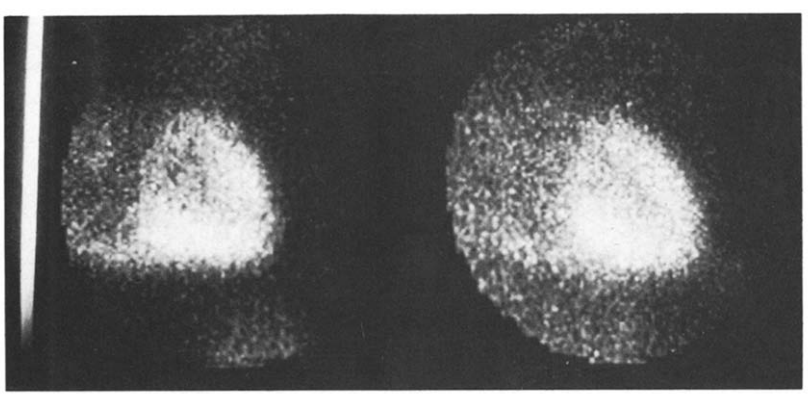


Figure 6. Patient 6. Stress **(left)** and redistribution **(right)** thallium scintigrams in the anterior view. During stress, uptake of thallium in the anterolateral segment is diminished. Uptake in this area is improved on the redistribution image.

ular myocardial tissue was abnormal in the 14 patients undergoing biopsy. However, in contrast to our cases, the thallium abnormalities persisted at rest in most of their patients, suggesting the presence of scar tissue rather than reversible cellular dysfunction.

Implications. Cellular membrane dysfunction should be considered a possible explanation for abnormal thallium myocardial images in some patients with normal coronary arteriograms. We believe that exertional hypoxemia is a probable cause of disordered cell function in this group of of patients with chronic pulmonary disease; this hypothesis warrants further study on a prospective basis.

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